

REMARKS

Reconsideration of this application is respectfully requested.

Claim 27 has been amended. Support for amended claim 27 can be found in previously presented claim 27 and in the specification:

Page 2, paragraph [0015] clearly establishes that the method of the invention needs a 3-D structure of the enzyme.

Page 7, paragraph [0104]: "..., the term "restrained dynamic docking" means a procedure by which the docking of the substrate is simulated"

Accordingly, entry of the Amendments is respectfully requested.

Sequence Rules compliance

The Examiner objected that the specification disclosed amino acid sequences greater than 4 bases in length not followed by a sequence identifier.

This objection has been obviated by amending the specification to refer to the sequences in Table 3 by their sequence identifiers. Thus, this objection may be withdrawn.

Rejections Under 35 U.S.C. § 112, 2nd paragraph

The Examiner rejected claims 27-30 and 33-39 under 35 U.S.C. § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention. More specifically, the Examiner states since claim 27 recites numerous steps starting with the letter j), the metes and bounds of the limitations are unclear as to where the previous steps (a-i) are or how they pertain to recited steps (j-s). The claim 27 has been amended by modifying the numbering of the method steps from j-s to A-J.

The Examiner also states that the limitation “docking of a substrate on an enzyme, a 3-D structure of which is available” in claim 27, is unclear as to whether the 3-D structure is available for the substrate, the enzyme, or the combination of substrate docked with the enzyme. Claim 27 has been amended to specify that the 3-D structure of said enzyme being available.

The Examiner also states that there is insufficient antecedent basis for the limitations “the other atoms” or “the mobile atoms”. Claim 27 has been amended to specify that “some other atoms are mobile, by allowing mobility of these mobile atoms”

The Examiner also states that there is insufficient antecedent basis for the limitation “the structure of the protein”. The claim 27 has been amended to modify the expression “the structure of the protein” by “the structure of the enzyme”.

The Examiner also states that there is no clear antecedent basis for the limitation “the atoms” in line 2 of step m and line 3 of step o, and for the limitation “the protein” in line 2 of step m. The claim 27 has been amended to modify:

the expression “the atoms of the protein” in line 2 of step D by “the atoms of the enzyme”; and

the expression “simulating an increase in temperature, in order to allow mobility of the atoms” in line 3 of step F by “simulating an increase in temperature, in order to allow mobility of all the atoms”

The Examiner also states that there is no clear antecedent basis for the limitation “the potential energy”. The claim 27 has been amended to modify the expression “the potential energy” by “the potential energy (Ep) in said force field of said 3-D structure”.

The Examiner also states that there is insufficient antecedent basis for the limitation “the backbone atoms N-C α -CO” in claim 28. Applicant respectfully disagrees. In fact, “the backbone atoms N-C α -CO” in claim 28 is clearly identified as the “fixed atoms in step B,” since claim 28 states that “said fixed atoms in step B are the backbone atoms N-C α -CO in the first minimization step and only C α in subsequent minimization steps”. Moreover, the expression “N-C α -CO” is well known to the skilled person as defining the peptide link. Thus, there is clearly a sufficient antecedent basis for this limitation.

The Examiner also states that the limitation “the C α ” in claim 28 is unclear. Applicant respectfully disagrees. In fact, the expression “C α ” refers to the alpha carbon of the peptide link “N-C α -CO”, which expression is well known to the skilled person.

The Examiner also states that the limitations “a”, “b”, “c”, “d”, “e”, “f” and “g” in claim 30 are unclear. The claim 30 has been amended to suppress these recitations.

Applicant submits that the rejection under 35 U.S.C. § 112, second paragraph, may be withdrawn.

Rejections Under 35 U.S.C. § 101

The Examiner rejected claims 27-30 and 33-39 under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. More specifically, the Examiner states that method claims 27-30 and 33-39 do not produce a tangible final result. In response to this rejection, Applicant has amended claim 27 to specify that the result generated in a readable format from this method for performing restrained dynamics docking of a substrate on an enzyme is a simulation of the docking of this

substrate on this enzyme. Consequently, the claimed method now recites that a specific result of the process is outputted to a user. Thus, the rejection under 35 U.S.C. §101 may be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner also rejected claims 27, 28, and 35 under 35 U.S.C. § 103(a) as being anticipated by Chang *et al.* in view of Di Nola *et al.* and in further view of Mager *et al.* This ground for rejection is respectively traversed and reconsideration is requested for the following reasons.

Chang *et al.* mainly discloses a method to identify enzymatic 3-D structures and, eventually, proposes, to use the GRAMM program in order to identify enzymatic binding site residues and enzymatic surface residues for redox partner interaction. Chang *et al.* does not disclose a method comprising two steps for minimizing the potential energy (Ep) linked to the force field of the 3-D structure of the enzyme, wherein in a first step (*i.e.*, B) the positions of some atoms of the enzyme are fixed and some other atoms are mobile, and wherein in a second step (*i.e.*, C) all the atoms of the enzyme are mobile.

Moreover, Chang *et al.* does not disclose two steps for minimizing the potential energy (Ep) linked to the force field of the 3-D structure of the enzyme obtained by (i) simulating an increase in temperature in order to give kinetic energy, and by (ii) minimizing the potential energy (Ep) linked to the force field of the 3-D structure by respecifying the temperature as 0 Kelvin (K).

Chang *et al.* further does not disclose the presence of a substrate next to the enzyme at 0 K.

Finally, Chang *et al.*, does not disclose a molecular dynamics simulation on the substrate and enzyme.

Di Nola *et al.* disclose a method for performing docking of substrates to proteins consisting of a dynamic simulation in which the center of mass motion is handled separately from the internal motion of the substrate molecule, and both types of motion are separately coupled to their own thermal baths. More specifically, Di Nola *et al.* discloses directly a step for minimizing the potential energy (E_p) linked to the force field of the complex (*i.e.*, phosphocholine-immunoglobulin complex) by 10 ps of MD simulation at $T = 300$ K followed by a 10 ps annealing of the temperature down to 10 K. Nevertheless, Di Nola *et al.* does not disclose a method comprising two steps for minimizing the potential energy (E_p) linked to the force field of the 3-D structure of the only enzyme, wherein in a first step (*i.e.*, B) the positions of some atoms of the enzyme are fixed and some other atoms are mobile, and wherein in a second step (*i.e.*, C) all the atoms of the enzyme are mobile, followed by a step (*i.e.*, E) of simulating the presence of the substrate next to the enzyme.

Finally, Di Nola *et al.* considers the center of motion of the substrate instead of the substrate itself for the simulation.

Mager *et al.* only discloses the conformational 3-D geometry of the Ω -loop of the Tyr181-Tyr188 segment from the HIV-1 reverse transcriptase and does not deal with docking of substrates at all. Thus, Mager *et al.* does not disclose any method for performing restrained dynamics docking of a substrate on an enzyme, a 3-D structure of the enzyme being available.

Moreover, Mager *et al.* only uses combined molecular-mechanical and quantum-mechanical approaches, but does not disclose suggest the steps of minimizing the potential energy (E_p) linked to the force field of the 3-D structure of the enzyme by (i) simulating an increase in temperature in order to give kinetic energy, and by (ii) minimizing the potential energy by respecifying the temperature at 0 K in order to minimize the potential energy linked to the force field. On the contrary, Mager *et al.* discloses molecular simulations at isothermal–isobaric conditions at a temperature of 0 Kelvin.

Considering the combination of these documents, Applicant respectfully observes that the Examiner has not provided any basis justifying why one of ordinary skill in the art would have combined these three documents so as to obtain the method of the invention.

Moreover, the teaching of Chang *et al.* in view of Di Nola *et al.* and of Mager *et al.* does not suggest any method for performing restrained dynamics docking of a substrate on an enzyme, wherein the minimization of potential energy (E_p) linked to the force field of the 3-D structure of the enzyme only is obtained by two successive steps, wherein in the first step (*i.e.*, B) the positions of some atoms of the enzyme are fixed and some other atoms are mobile, and wherein in a second step (*i.e.*, C) all the atoms of the enzyme are mobile, followed by a step (*i.e.*, E) of simulating the presence of the substrate next to the enzyme.

Moreover, none of these documents discloses specifically steps of minimizing the potential energy (E_p) linked to the force field of the 3-D structure of the enzyme only by (i) simulating an increase in temperature in order to give kinetic energy and by (ii)

minimizing the potential energy by respecifying the temperature at 0 K in order to
minimize the potential energy linked to the force field

For these reasons, Applicant respectfully submits that a *prima facie* case of
obviousness has not been established. Thus, the rejection under 35 U.S.C. §103
should be withdrawn.

If there are any fees due in connection with the filing of this Amendment, please
charge the fees to Deposit Account No. 06-0916.

Respectfully submitted,

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